A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence

Objectives: **This study compared 24-, 48-, 72-, and 96-hour buprenorphine dosing regimens in opioid-dependent outpatients.**

Methods: **Fourteen subjects received buprenorphine in a double-blind, placebo-controlled crossover trial. Daily sublingual maintenance doses were 4 mg/70 kg (n = 5) and 8 mg/70 kg (n = 9). After a stabilization period of maintenance administration, subjects received, in a random order, four dosing regimens for five repetitions of each regimen: a maintenance dose every 24 hours, a doubled maintenance dose every 48 hours, a tripled maintenance dose every 72 hours, and a quadrupled maintenance dose every 96 hours. In the latter three dosing regimens, subjects received placebo on the interposed day(s). Study participation was contingent on opioid abstinence and daily clinic attendance. Measures of subjective opioid agonist and withdrawal effects were assessed daily.**

Results: **Relative to standard maintenance dosing, none of the higher doses induced agonist effects. Changes in indices of subjective withdrawal effects were noted as the time since the last active dose increased during intermittent dosing regimens, but the magnitude of these effects was relatively low and was comparable to those found in other alternate-day dosing studies.**

Conclusions: **These results support the feasibility and safety of twice weekly buprenorphine dosing regimens. (Clin Pharmacol Ther 1999;66:306-14.)**

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According to the National Institute on Drug Abuse,[1] the most effective intervention preventing the spread of human immunodeficiency virus is methadone maintenance, which reduces both opioid and other drug use.[2-4] Despite its benefits, methadone has some drawbacks. As a full opioid agonist, methadone has significant abuse liability and can induce respiratory depression,[5] resulting in overdose and death.[6]

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Because of these issues, federal regulations require frequent (6 to 7 days per week) clinic attendance. This frequent dosing schedule, however, may serve as an obstacle in treatment,[7] especially among patients with work or child care responsibilities. Daily dosing also is a burden for treatment facilities, some of which provide doses for more than 900 patients daily. Patients taking methadone prefer take-home doses, but they are often associated with medication diversion.[8-9] If attendance of less than once a day could be arranged without the provision of take-home medications, more patients may enter and remain in treatment without the risks of diversion and overdose.

Buprenorphine is still an experimental medication for the treatment of opioid dependence, but approval by the Food and Drug Administration (FDA) is expected soon, and it is already available in some European countries. Buprenorphine is a high affinity partial μ-opioid agonist with a long duration of action.[10-11] Buprenorphine is comparable to methadone in retaining patients in maintenance and in detoxification trials.[12-15] It also has some advantages over methadone. Most notably, buprenorphine has a ceiling level on ago-

nist activity, limiting adverse reactions at doses as high as 100 times the analgesic dose.[16-19]

Several studies have investigated alternate-day buprenorphine administration. One study[20] randomly assigned one group of opioid-dependent inpatients to receive an 8 mg dose every day, whereas another group received the same dose every other day with placebo on the intervening day. No differences emerged between the two groups on measures of withdrawal, but among those receiving alternate-day dosing, reports of "urges" for opioids and dysphoria increased on days after placebo administration compared with reports obtained on days after active doses. These findings were replicated in a larger outpatient study.[21] Compared with subjects receiving the daily dosing regimen, subjects receiving doses every other day reported more withdrawal symptoms, submitted more opioid-positive urine samples, and withdrew from treatment at a higher rate. These data suggest that less frequent dosing may not be efficacious with use of a standard buprenorphine dose.

Because high buprenorphine doses do not result in increased opioid effects,[19,22] the partial agonist profile of this drug suggests the possibility of increasing the dosage to allow for longer dosing intervals. In previous studies, we have shown that doubling the maintenance dose (eg, 16 mg/70 kg) prevents subjective withdrawal symptoms for a 48-hour period,[23-24] and tripling the maintenance dose (eg, 24 mg/70 kg) can suppress significant withdrawal symptoms for up to 72 hours,[25] allowing for a dosing regimen of three times a week. In detoxification trials with use of buprenorphine, we routinely allow subjects to choose an attendance schedule of 7 days per week, 4 days per week, or 3 days per week. Only 12% chose daily attendance, whereas 36% chose 4 days per week and 52% chose 3 days per week. Therefore a dosing regimen of three times a week is preferred to daily dosing by most opioid-dependent outpatients.

Given the efficacy and acceptability of tripled buprenorphine dosing regimens, this study was designed as the first of a series to investigate the feasibility of quadrupled buprenorphine doses administered every 4 days. In this study, we compared four buprenorphine dosing regimens with use of a double-blind, placebo-controlled within-subject design.

METHODS

Subjects

Twenty-six outpatients (20 men and six women) were enrolled in the study; 14 (11 men and three women) completed the study. Subjects were included if they met the following criteria; were >18 years old, in good health, met DSM-III-R criteria for opioid dependence, and met FDA criteria for methadone treatment. Health status was determined by history, physical examination, and laboratory evaluation (including electrocardiogram, complete blood cell count, clinical chemistry profiles, and urinalyses). Evidence of active psychosis or serious medical illness were exclusion criteria. Other drug dependence did not exclude subjects from participation. The study was approved by the Institutional Review Board, and all subjects provided informed consent.

The mean age of the subjects was 38 years (age range, 23 to 51 years), and mean weight was 82 kg (weight range, 54 to 112 kg). Subjects reported using opioids regularly for an average of 12 years (range, 1 to 31 years) and spending $320 (range, $23 to $840) per week on opioids. Eighty-eight percent of the subjects were intravenous drug users. Weekly pregnancy tests were conducted with the female subjects, and these were negative throughout the study.

Procedures

Study continuation and compensation ($50 per week) were contingent on daily attendance and opioid abstinence. Subjects were required to attend the clinic at the same time each day to facilitate a 24-hour dosing schedule. Opioid abstinence was confirmed through urinalysis testing conducted three times a week with staff observation. Urine results were analyzed for the presence of opioids (opioids, methadone, and propoxyphene [INN, dextropropoxyphene]) with use of the Enzyme Multiplied Immunoassay Technique (Syva Corp, San Jose, Calif). If a subject submitted an opioid-positive urine sample, no medication was provided that day. Data collected in the days since the last negative urine sample were omitted from analyses.

Subjects continued to participate in the study if the next urinalysis test indicated no further opioid use. Study participation was terminated after submission of a second opioid-positive sample.

One urine sample collected each week was randomly selected and screened for use of other drugs. No contingencies were placed on non-opioid drug use, but subjects were not permitted to attend the clinic if they were intoxicated. Sobriety tests were conducted if intoxication was suspected, and breath alcohol samples were collected on urine testing days. Subjects participated in weekly 60-minute counseling sessions.[26]

Medication administration

Buprenorphine hydrochloride (Reckitt and Colman, Hull, England) was prepared as a stock concentration of 16 mg/mL in 35% ethanol (vol/vol). Stock solutions containing 2, 4, and 8 mg/mL in 35% ethanol (vol/vol)

Table I. Mean and SEM (in parentheses) values of outcome data across the different dosing conditions

		Maintenance dose	*Doubled maintenance dose*		*Tripled maintenance dose*		
Measure	*Maximum*	*24 Hours*	*24 Hours*	*48 Hours*	*24 Hours*	*48 Hours*	*72 Hours*
Observer							
Withdrawal	9	0.23 (0.04)	0.23 (0.04)	0.22 (0.07)	0.24 (0.06)	0.23 (0.06)	0.30 (0.07)
Agonist	9	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
ARS							
Withdrawal	9	2.24 (0.50)	2.19 (0.46)	2.53 (0.49)	1.93 (0.44)	2.92 (0.43)	3.16 (0.48)*
Drug/agonist	9	0.72 (0.18)	0.65 (0.19)	0.68 (0.18)	0.83 (0.18)	0.69 (0.18)	0.75 (0.21)
VAS							
High	100	6.9 (3.3)	5.2 (2.6)	3.7 (1.5)	6.9 (3.4)	5.8 (3.1)	6.2 (2.6)
Drug	100	14.8 (3.7)	14.3 (2.8)	7.4 (2.2)*	15.9 (3.5)	9.3 (3.7)	10.4 (4.7)
Good	100	17.4 (4.7)	16.2 (2.8)	7.2 (1.8)*	20.5 (4.9)	9.9 (4.1)	12.9 (5.2)
Like	100	24.1 (4.6)	20.8 (4.5)	18.5 (4.5)	24.3 (4.8)	18.5 (4.5)	19.8 (5.7)
Bad	100	10.4 (3.3)	11.3 (3.7)	12.2 (3.8)	9.4 (3.6)	13.1 (4.0)	16.4 (4.3)
Sick	100	27.1 (5.9)	20.2 (4.2)	25.6 (3.7)	18.5 (4.3)	30.5 (4.3)	35.2 (4.5)
ARCI							
PCAG	15	5.3 (0.8)	6.1 (0.8)	7.8 (0.8)*	5.4 (0.7)	7.7 (0.8)*	8.6 (0.8)*
LSD	13	4.8 (0.5)	5.4 (0.6)	6.2 (0.7)	4.9 (0.4)	7.0 (0.5)*	6.7 (0.7)*
MBG	14	3.5 (1.1)	3.4 (1.1)	2.0 (0.6)	3.8 (1.0)	1.9 (0.4)	1.2 (0.4)*
BG	16	5.5 (0.8)	5.1 (0.8)	3.7 (0.6)	5.4 (0.7)	3.8 (0.5)	3.1 (0.8)*
A	11	3.0 (0.7)	3.0 (0.7)	2.1 (0.4)	3.1 (0.8)	2.3 (0.4)	1.5 (0.3)*
Dose ID (mean % guessed)							
Placebo	100	26 (5)	16 (6)	67 (9)*	19 (4)	66 (11)*	66 (10)*
>Maintenance dose	100	18 (8)	36 (7)	13 (6)	46 (7)*	14 (8)	14 (7)
Pupil diameter (mm)		5.9 (0.2)	5.5 (0.2)*	6.0 (0.2)	5.5 (0.2)*	5.8 (0.2)	5.9 (0.2)

ARS, Adjective rating scale; VAS, visual analog scales; ARCI, Addiction Research Center Inventory; PCAG, pentobarbitol, chlorpromazine, alcohol group; LSD, lysergic acid diethylamide; MBG, morphine benzedrine group; BG, benzedrine group; A, amphetamine.
*Significantly different from maintenance dose ($P < .05$) with use of Dunnett's procedure.

were prepared from dilutions of the 16 mg/mL stock. Placebo consisted of ethanol vehicle. The maximum volume necessary for the highest dose was calculated based on weight on an individual basis, and doses were delivered in a constant volume throughout the study. Subjects held the medication under their tongues for 5 minutes. Medications were administered with Ped-Pod Oral Dispensers (SoloPak Laboratories, Franklin Park, Ill) under double-blind conditions and were masked for taste with 1 mL of Bitrex granules (6 μg/mL; Macfarlan-Smith Ltd, Edinburgh, Scotland) and peppermint. Subjects swished the solution in their mouths for 30 seconds and discarded it before receiving medication.

Subjects received a 2 mg/70 kg dose when they came to the clinic and a 4 mg/70 kg dose on day 2. If withdrawal symptoms were evident on days 3 through 7, the dose was increased to 8 mg/70 kg. Eight subjects (five completers) received a 4 mg/70 kg sublingual maintenance dose, and 18 subjects (nine completers) received an 8 mg/70 kg sublingual maintenance dose.

Subjects were instructed that they would receive buprenorphine daily, every other day, every third day, or every fourth day throughout the study. Subjects were also informed that when they received buprenorphine on alternate days, they would receive two, three, or four times their daily maintenance doses with placebo on the interposed day(s).

Laboratory safety session

The sublingual maintenance dose was administered for 10 consecutive days (days 8 to 17). On day 18, subjects participated in a laboratory session in which they were exposed to four times their maintenance doses (16 or 32 mg/70 kg) to ensure the safety of, and tolerance to, this dose of buprenorphine. After baseline collection of physiologic parameters (heart rate and blood pressure), psychomotor performance (digit symbol substitution test [DSST][27]), and observer and subjective indicators of opioid agonist and withdrawal effects (see below), subjects received double their maintenance doses. Each subject received a standard sublingual maintenance dose 1½ hours later, for a total cumulative dose of three times the maintenance dose. After another 1½ hours, each subject received another maintenance dose, for a total cumulative dose of four times their maintenance doses. Physiologic indices, psychomotor performance, and observer and subjective indicators of opioid agonist and withdrawal effects were collected at

Quadrupled maintenance dose			
24 Hours	*48 Hours*	*72 Hours*	*96 Hours*
0.21 (0.05)	0.22 (0.03)	0.27 (0.08)	0.33 (0.07)
0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
1.60 (0.39)	2.23 (0.48)	2.66 (0.49)	3.43 (0.55)*
0.76 (0.16)	0.56 (0.15)	0.58 (0.17)	0.58 (0.15)
5.37 (2.0)	4.0 (1.9)	4.1 (2.4)	4.6 (2.6)
15.2 (2.9)	7.3 (2.8)*	7.4 (2.7)*	7.0 (2.8)*
17.8 (3.6)	10.1 (3.5)	8.6 (3.4)*	9.0 (3.5)*
27.9 (5.9)	20.4 (5.7)	15.2 (3.8)*	18.1 (6.3)
9.2 (4.1)	12.0 (3.9)	13.1 (4.1)	14.6 (3.9)
19.2 (4.9)	27.0 (4.2)	34.3 (5.1)	45.7 (5.5)*
4.9 (0.6)	6.6 (0.7)	7.4 (0.8)	7.8 (0.9)*
5.1 (0.7)	6.4 (0.6)	7.1 (0.6)*	7.3 (0.8)*
3.9 (1.1)	2.1 (0.7)	1.6 (0.5)	1.2 (0.3)*
5.7 (0.9)	4.3 (0.7)	3.4 (0.6)*	3.3 (0.6)*
3.3 (0.7)	2.4 (0.5)	1.8 (0.4)	1.5 (0.3)*
6 (4)	64 (11)*	62 (10)*	69 (9)*
49 (9)*	12 (7)	17 (8)	13 (7)
5.5 (0.2)*	5.7 (0.2)	5.9 (0.2)	6.1 (.2)

30-minute intervals throughout the session. If a subject were to exhibit opioid agonist effects, she or he would have been removed from the study and enrolled in another protocol that did not require such large doses.

Open dosing exposure

During the 4 days after the laboratory session, subjects received maintenance doses under double-blind conditions. On days 5 to 7 after the laboratory session, subjects again received a maintenance dose daily, but for these 3 days the dose was provided under open conditions and subjects were told they were receiving their maintenance doses at dispensation. These 3 days were included to allow subjects to experience how they felt when they knew they were receiving their daily maintenance doses. After this open-dosing exposure, subjects received maintenance doses for the next 10 days under double-blind procedures.

Random assignment to dosing regimens

Beginning 18 days after the laboratory session, exposure to each of the four dosing regimens began. Subjects received each of the four regimens in a random order: their maintenance doses daily, doubled doses every other day with placebo on the interposed day, tripled doses every third day with placebo on the interposed 2 days, and quadrupled doses with placebo on the interposed 3 days. Each dosing regimen was kept in effect for five repetitions so that the maintenance regimen was in effect for 5 days, the doubled dose regimen for 10 days, the tripled dose regimen for 15 days, and the quadrupled dose regimen for 20 days. After exposure to the different dosing regimens, subjects received maintenance doses for 5 days. Subjects could then transfer to other ongoing buprenorphine studies or to a detoxification.

Dependent measures

Observer ratings. The research staff (blinded to the treatment conditions) completed an observer-rating scale daily before medication was dispensed. The staff rated subjects on a scale from 0 (not at all) to 9 (severe) on signs of opioid withdrawal (gooseflesh, sweating, restlessness, tremor, lacrimation, nasal congestion, and yawning) and agonist activity (skin itching, vomiting, sedation, nodding, and soapboxing/nodding). The observer-rating scale was based on Addiction Research Center withdrawal scales.[17,28]

Subject ratings. Each day before receiving medication, subjects completed an adjective rating scale (ARS), visual analog scale (VAS), the Addiction Research Center Inventory (ARCI) short form, and a dose-identification question. Subjects were instructed to respond to questions according to their experiences during the previous 24 hours.

The ARS[12,16] consists of 32 opioid withdrawal and drug symptoms. Subjects rated each item according to a scale from 0 (none) to 9 (severe), and mean values across all items are shown. The following items were included in the opioid withdrawal scale: muscle cramps, depressed/sad, painful joints, yawning, hot or cold flashes, trouble getting to sleep, sick stomach, runny nose, poor appetite, weak knees, abdominal cramps, tense/jittery, excessive sneezing, irritable, watery eyes, and fitful sleep. The following items were included in the opioid effects scale: drug effect, loaded/high, rush, flushing, sweating, nodding, dry mouth, stomach turning, itchy skin, relaxed, coasting/spaced out, talkative, pleasant sickness, drive, nervousness, and drunk.

The following items were included in the VAS[29-30]: high, drug, good, like, bad, and sick. Subjects made a mark along a 100 mm line, anchored at each end by "not at all" and "severe." Responses were converted to a 100-point scale.

The ARCI short form[31-32] consisted of 49 true/false items. Five scales assessed sedation, dysphoria, eupho-

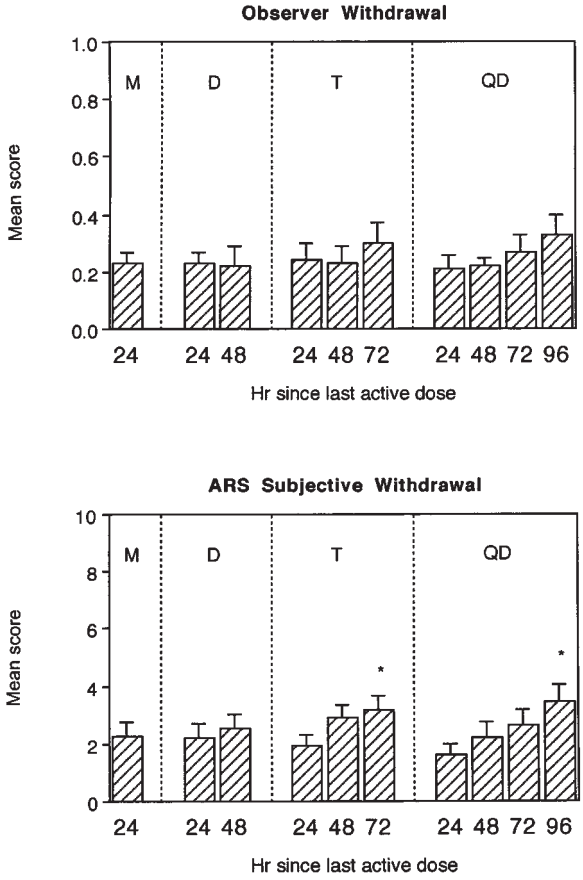

Fig 1. Top panel, Observer-rated withdrawal symptoms are shown across the four different dosing regimens according to hours since the last active dose. Values represent mean values and SD. Variables showing withdrawal effects are depicted by *hatched bars*. **Bottom panel,** Adjective-rating scale subjective withdrawal symptoms are shown across the four different dosing regimens according to hours since the last active dose. Values represent mean values and SD. M, Sublingual maintenance doses; D, doubled maintenance dose; T, a tripled maintenance dose; QD, quadrupled maintenance dose.

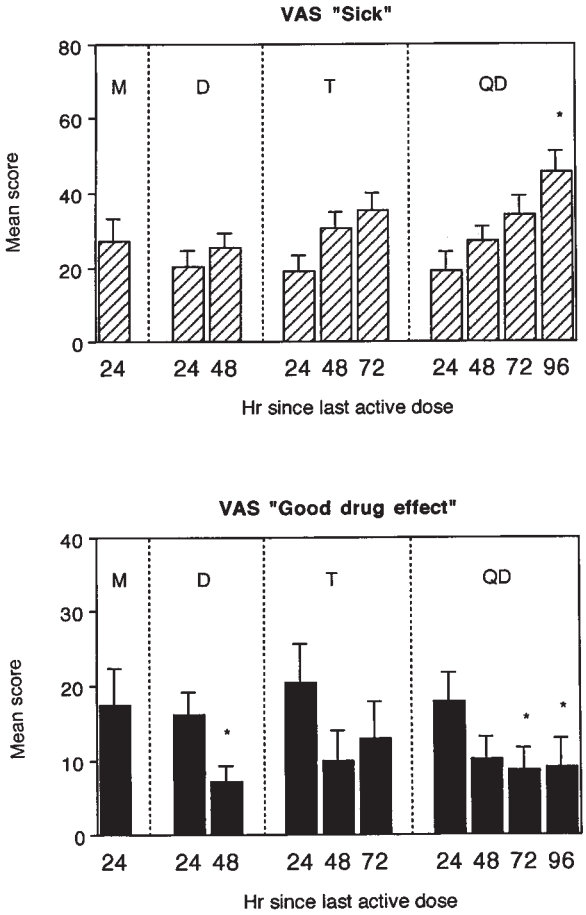

Fig 2. Top panel, Visual analog scale (VAS) "sick" scores are shown across the four different dosing regimens according to hours since the last active dose. Values represent mean values and SD. **Bottom panel,** VAS "good drug effect" scores are shown across the four different dosing regimens according to hours since the last active dose. Values represent mean values and SD. Variables showing agonist effects are depicted by *solid bars.*

ria, and stimulation: pentobarbitol, chlorpromazine, alchohol group (PCAG), lysergic acid diethylamide (LSD), morphine benzedrine group (MBG), benzedrine group (BG), and amphetamine (A).

Subjects indicated whether they received placebo or a maintenance, doubled, tripled, or quadrupled dose the previous day. Results were scored as identification of (1) placebo or (2) higher than maintenance dose.

Pupil diameter. Pupil diameter was determined before medication was dispensed from photographs taken with a Polaroid camera (Polaroid Corp, Cambridge, Mass) at original magnification ×2 at 1 footcandle of ambient illumination.[33]

Urinalysis testing. Urinalysis testing was conducted three times a week for opioids, and one sample per week was screened for other drugs: benzodiazepines, barbiturates, marijuana, and cocaine.

Data analysis

Data obtained during the doubled, tripled, and quadrupled dose regimens were partitioned into individual components for analyses (eg, hours since last active dose). In total, 10 conditions were obtained: 24 hours after the maintenance dose, 24 hours after the doubled

dose, 48 hours after the doubled dose, 24 hours after the tripled dose, 48 hours after the tripled dose, 72 hours after the tripled dose, 24 hours after the quadrupled dose, 48 hours after the quadrupled dose, 72 hours after the quadrupled dose, and 96 hours after the quadrupled dose. For the 14 study completers, repeated-measures ANOVA was conducted with one within-subject factor (condition, with 10 levels) and one between-subject factor (maintenance dose, with two levels). When the overall F test corresponding to conditions was significant ($P < .05$), Dunnett's procedure was used to determine whether measures obtained during the nine experimental conditions differed from the 24-hour post-maintenance dose condition. Analyses were performed with use of SAS (SAS Institute, Cary, NC), and statistical significance was determined with $\alpha = .05$.

Descriptive data are presented for the percentage of urine samples obtained that were positive for opioids and other drugs across dosing regimens. We cannot assess the exact day of drug use because urine samples were obtained three times a week. Data are therefore shown across entire dosing regimens (percentage of positive during maintenance, doubled, tripled, and quadrupled dosing regimens). Because submission of opioid-positive samples resulted in study termination, urinalyses data are presented from all subjects enrolled, including noncompleters.

RESULTS

Fifty-four percent of the subjects completed the study. Four subjects discontinued because of transportation problems, and three withdrew because they moved out of state. Another five were discharged for submitting more than one opioid-positive urine specimen. Among these, two subjects tested positive for opioids during baseline and the doubled dose regimen and two during the doubled and tripled dose regimens, and another subject used opioids twice during the tripled dose regimen.

Because no significant effect of buprenorphine dose (4 mg/70 kg versus 8 mg/70 kg) was found for any of the outcome measures, Table I displays summary statistics for all outcome measures across the 10 conditions, collapsing across the buprenorphine dose. No differences on observer ratings of withdrawal were noted across conditions, but significant differences were found on 10 of the 13 self-reported measures. On the ARS, withdrawal symptoms differed among the conditions ($F_{9,108} = 6.52$; $P < .001$). On the VAS, significant differences were noted on the "drug," "good," "like," and "sick" items ($F_{9,108} = 4.53$, $F_{9,108} = 5.54$, $F_{9,108} = 8.45$, and $F_{9,108} = 3.76$, respectively; $P < .001$). Significant differences were observed on all the ARCI scales ($F_{9,108} = 3.3$ to $F_{9,108} = 4.98$; $P < .001$). The mean percentage of times subjects guessed that they received a placebo dose the previous day also differed among conditions ($F_{9,108} = 19.8$; $P < .001$), as did the percentage of times the doses were identified as greater than the sublingual maintenance dose ($F_{9,108} = 8.45$, $P < .001$). Pupil diameter also differed across conditions ($F_{9,108} = 6.33$; $P < .001$). The remainder of this section details differences between maintenance dosing and the other conditions using Dunnett's procedure.

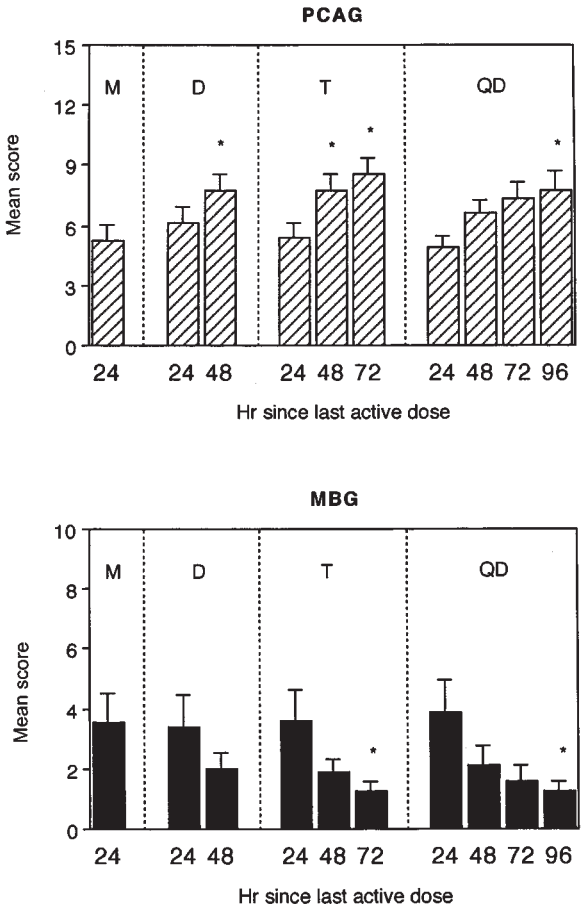

Fig 3. Top panel, Addiction Research Center Inventory PCAG scores assessing sedation are shown across the four different dosing regimens according to hours since the last active dose. Values represent mean values and SD. **Bottom panel,** Addiction Research Center Inventory MBG scores assessing euphoria are shown across the four different dosing regimens according to the hours since the last active dose. Values represent mean values and SD.

Doubled dose regimen

No significant differences were noted when subjective outcome data obtained 24 hours after the maintenance doses were compared with that obtained 24 hours

Table II. Percentage of urine samples that were positive for opioids, barbiturates, benzodiazepines, tetrahydrocannabinol, and cocaine across the four dosing regimens

	Opioids	*Barbiturates*	*Benzodiazepines*	*Tetrahydrocannabinol*	*Cocaine*
Maintenance dosing	11%	7%	50%	27%	13%
Doubled maintenance dose	9%	8%	47%	36%	13%
Tripled maintenance dose	4%	13%	60%	40%	14%
Quadrupled maintenance dose	6%	12%	56%	47%	19%

after the doubled doses. Data obtained 48 hours after doubled doses, however, did differ from data obtained after maintenance doses on the VAS "drug" and "good" items and PCAG ratings on the ARCI. Figs 1 through 3 show mean scores on some outcome measures across the conditions.

The average percentage of times subjects correctly identified placebo doses during the doubled dose regimen was significantly higher than placebo identifications during sublingual maintenance dosing. Pupil diameter was significantly smaller 24 hours after doubled doses compared with 24 hours after maintenance doses, but pupil diameter 48 hours after doubled doses did not differ from that 24 hours after maintenance doses.

Tripled dose regimen

Subjective measures of opioid agonist and withdrawal effects did not differ between 24 hours after maintenance dosing and 24 hours after the tripled dose regimen. Comparison of two indices (PCAG and LSD scales of the ARCI) 24 hours after maintenance doses and 48 hours after the tripled dose regimen showed significant differences, and six of 13 subjective report measures differed when comparing data obtained after maintenance doses with that obtained 72 hours after the tripled dose regimens. These included the withdrawal scores on the ARS and all five of the ARCI scales.

Subjects identified tripled doses to be greater than maintenance doses a greater proportion of the time than they identified maintenance doses to be greater than maintenance doses. They were also more likely to correctly identify placebo doses during the tripled dose regimen. Pupil diameters were significantly smaller 24 hours after tripled doses than 24 hours after maintenance doses.

Quadrupled dose regimen

No differences in subjective or observer ratings were noted for comparison of data obtained during the maintenance dose regimen to that obtained 24 hours after a quadrupled dose, and only the "drug" item of the VAS differed between daily maintenance doses and 48 hours after quadrupled doses. In comparing subjective data obtained 72 hours after quadrupled doses to that obtained 24 hours after maintenance doses, five of 13 significant differences emerged. On the VAS, the "drug," "good," and "like" scores were all lower 72 hours after quadrupled doses compared with 24 hours after sublingual maintenance doses. On the ARCI, BG scores were lower and LSD scores were higher. Data obtained 96 hours after quadrupled doses differed from that obtained 24 hours after maintenance doses on the majority of subjective indicators of drug and withdrawal effects. Differences in pupil diameter and dose identification were what we expected.

Table II shows percentage of urine samples positive for drugs across the dosing regimens. Only 4% to 11% of samples were opioid positive, and these values did not vary across the regimens. These percentages include data from subjects who were discharged from the study because of opioid use. The frequency of other drug use did not differ systematically across dosing regimens. No positive breath alcohol samples were obtained.

DISCUSSION

This study examined whether administration of four times the maintenance dose of buprenorphine induced opioid agonist effects and whether alternate-day dosing regimens, with dosing as infrequently as every 4 days, were able to abate withdrawal. This study provides support for the safety and feasibility of twice-a-week buprenorphine dosing regimens.

In terms of safety, no subjects exhibited opioid agonist effects when exposed to quadrupled doses in the laboratory session, and statistically significant increases in opioid agonist effects did not emerge when quadrupled doses were provided. For example, self-reports of "high" on a 100-point scale were 7 after sublingual maintenance doses and 5 after quadrupled doses. On the VAS "good" scale, self-reports were 17 after maintenance doses and 18 after quadrupled doses. The MBG scale of the ARCI is a sensitive indicator of opioid agonist effects.[31,32] A mean of 3.5 (on a 14-point scale) was obtained after maintenance doses compared with a

mean of 3.9 after quadrupled doses. Drug effects on the ARS were also similar between maintenance and quadrupled dosing conditions, with mean values of 0.7 and 0.8, respectively. Therefore subjective reports of opioid agonist activity did not occur when subjects received up to 32 mg/70 kg buprenorphine.

A criticism of these data is that subjective reports of agonist activity were obtained 24 hours after dose administration, but peak onset of drug effects occurs approximately 2 hours after sublingual administration. Therefore subjects might have experienced agoinst activity, yet not reported it the next day. However, all subjects were exposed to quadrupled doses during controlled laboratory procedures, and subjective and objective indicators of agonist effects, as well as psychomotor performance and physiologic effects, were obtained throughout a 4-hour session. None of the subjects had any agonist effects in these sessions. These findings of limited opioid agonist effects are consistent with buprenorphine's profile as a partial agonist with a wide margin of safety.[10,17-19]

This study also replicated and extended previous findings of administration of doubled doses every 48 hours[23-24] and tripled doses every 72 hours.[25] These previous studies showed that drug effects diminish and withdrawal effects intensify as the time since the active dose increases. In our study, drug effects likewise decreased as days since the last active dose increased. For example, mean scores on the drug effects item were 15 after maintenance doses and decreased significantly to 7 when measured 48 hours after doubled doses or 48 to 96 hours after quadrupled doses.

As in previous studies,[23-25] this study showed increases in subjective reports of opioid withdrawal as time since the last active dose increased. ARS withdrawal scores increased from a mean of 2.2 after the sublingual maintenance doses to 3.2 measured 72 hours after tripled dosing and 3.4 measured 96 hours after quadrupled dosing. The mean score on the VAS sick scale increased from 27 after maintenance doses to 46 in the 96 hours after quadrupled doses. Although these changes reflect an increase in subjective reports of withdrawal, the magnitude of the effects may be of limited clinical significance. No changes in observer ratings of withdrawal were noted across conditions, and pupil diameter, a sensitive indication of opioid withdrawal, never increased significantly. The magnitude of withdrawal experienced 96 hours after quadrupled doses was similar to that 48 hours after doubled doses.[24] Despite these increases in subjective reports of withdrawal during alternate-day dosing regimens, 96% of subjects chose the doubled dose regimen over daily maintenance dosing.[24]

This study evaluated the feasibility of quadrupled dosing during blinded dosing conditions, but another study found that subjects experienced similar levels of withdrawal when exposed to these dosing regimens during open-dosing procedures and that 46% of subjects preferred the quadrupled dose regimen over any other (Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens using open-dosing procedures: is twice weekly dosing possible? Submitted for publication). Although one could argue that subjects may use other drugs to abate opioid withdrawal during the every-fourth-day regimens, no systematic differences in other drug use were noted across the regimens.

Treatment compliance and retention are variables with important clinical relevance. This study, mandating 7-day-a-week attendance and abstinence from all other forms of opioids, is not able to address how well patients would tolerate quadrupled dose regimens when provided under open-dosing procedures, or when opioid abstinence was not required. Despite the burdens this study placed on subjects, few subjects submitted opioid-positive urine samples. The transportation burden was another common reason for study termination and one that an alternate-day schedule would diminish.

Other studies have shown that take-home doses[34] and alternate-day dosing schedules[24] can be reinforcers for abstinence among opioid-dependent patients. If quadrupled dose regimens, when applied under open-dosing procedures, do not induce significant opioid agonist effects and serve as reinforcers, this dosing schedule would permit twice-per-week clinic attendance (eg, Monday and Friday), without the provision of take-home doses. This schedule may increase the ability of clinics to serve more patients without a proportional increase in staff. It may also attract more patients to treatment.

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References

1. Council on Addiction Psychiatry. Position statement on methadone maintenance treatment. Am J Psychiatry 1994;151:792-4.
2. Ball JC, Ross A. The effectiveness of methadone maintenance treatment. New York: Springer-Verlag; 1991.
3. Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, et al. Human immunodeficiency virus

seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr 1993;6:1049-56.
4. Saxon AJ, Calsyn DA, Jackson TR. Longitudinal changes in injection behaviors in a cohort of injection drug users. Addiction 1994;89:191-202.
5. Liguori A, Morse WH, Bergman J. Respiratory effects of opioid full and partial agonists in rhesus monkeys. J Pharmacol Exp Ther 1996;277:462-72.
6. Neeleman J, Farrell M. Fatal methadone and heroin overdoses: time trends in England and Wales. J Epidemiol Community Health 1997;51:435-7.
7. Pani P, Pirastu R, Ricci A, Gessa G. Prohibition of take-home dosages: negative consequences on methadone maintenance treatment. Drug Alcohol Depend 1996;41:81-4.
8. Goldman FR, Thistel CI. Diversion of methadone: illicit methadone use among applicants to two metropolitan drug abuse programs. Int J Addict 1978;13:855-62.
9. Kim TF. Methadone maintenance treatment remains controversial even after 23 years of experience. JAMA 1988; 260:2970-5.
10. Bickel WK, Amass L. Buprenorphine treatment of opioid dependence: a review. Exp Clin Psychopharmacol 1995;3:477-89.
11. Rance MJ, Dickens JN. The influence of drug-receptor kinetics on the pharmacological and pharmacokinetic profiles of buprenorphine: In: Van Ree JM, Pereniums L, editors. Characteristics and function of opioids. Amsterdam: Elsevier; 1978. p. 65-6.
12. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. Clin Pharmacol Ther 1988;43:72-8.
13. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA 1992;267:2750-5.
14. Ling W. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry 1996;53:401-7.
15. Kosten TR, Shottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. J Nerv Ment Dis 1993;181:358-64.
16. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski D, Johnson R. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. J Pharmacol Exp Ther 1988;247:47-53.
17. Jasinski DR, Pevnick J, Griffith J. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 1978;35:501-16.
18. Lange WR, Fudala PJ, Dax EM, Johnson RE. Safety and side-effects of buprenorphine in the clinical management of heroin addiction. Drug Alcohol Depend 1990;26:19-28.
19. Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. J Pharmacol Exp Ther 1995; 274:361-72.
20. Fudala PJ, Jaffe J, Dax E, Johnson RE. Use of buprenorphine in the treatment of opioid addiction: physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin Pharmacol Ther 1990;47:525-34.
21. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. Drug Alcohol Depend 1995;40:27-35.
22. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther 1994;55:569-80.
23. Amass L, Bickel WK, Higgins ST, Badger G. Alternate-day dosing during buprenorphine treatment of opioid dependence. Life Sci 1994;54:1215-28.
24. Amass L, Bickel WK, Crean JP, Blake J, Higgins ST. Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. Psychopharmacology (Berl) 1998;136:217-25.
25. Bickel WK, Amass L, Badger GJ. A double-blind controlled trial of buprenorphine dosing every 72 hours in opioid-dependent humans. Psychopharmacology (Berl) [in press].
26. Bickel WK, Amass L, Higgins ST, Badger GJ, Esch RA. Effects of behavioral treatment during opioid detoxification with buprenorphine. J Consult Clin Psychol 1997;65: 803-10.
27. McLeod D, Griffiths RR, Bigelow GE, Yingling J. An automated version of the digit symbol substitution test (DSST). Behav Res Methods Instrum 1982;14:463-6.
28. Himmelsbach CK. Studies of certain addiction characteristics of (a)dihydromorphone. J Pharmacol Exp Ther 1939;67:239-49.
29. Preston KL, Bigelow GE, Liebson IA. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. Psychopharmacology (Berl) 1988;94:484-90.
30. Petry NM, Bickel WK, Huddleston J, Tzanis E, Badger GJ. A comparison of subjective, psychomotor and physiological effects of a novel muscarinic analgesic, LY297802 tartrate, and oral morphine in occasional drug users. Drug Alcohol Depend 1998;50:129-36.
31. Jasinski DR. Assessment of the abuse potentiality of morphine like drugs (methods used in man). In: Martin WR, editor. Drug addiction. New York: Springer-Verlag; 1977. p. 197-258.
32. Martin W, Sloan JW, Shapiro JD, Jasinski DR. Physiologic, subjective and behavioral effects of amphetamine, metamphetamine, ephendrine, phenmetrazine and methylphenidate in man. Clin Pharmacol Ther 1971;12: 245-58.
33. Jasinski DR, Martin WR. Evaluation of a new photographic method for assessing pupil diameters. Clin Pharmacol Ther 1967;8:271-2.
34. Stitzer ML, Iguchi M, Felch L. Contingent take-home incentive: effects on drug use of methadone maintenance patients. J Consult Clin Psychol 1992;60:927-34.